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COMPARISON AND EVALUATION OF PREPARATIVE METHODS.

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**CNE-CARBON ¹³C-LABELED SYNTHETIC INTERMEDIATES.
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ABSTRACT

Frequently the biggest stumbling block to the synthesis of a structurally complex labeled compound is obtaining the required low molecular weight, structurally simple, isotopic intermediates. Many are becoming commercially available or can be obtained by custom synthesis; however, for certain applications or for some investigators the time required or the cost may be prohibitive. Even though facilities and skills are usually available within the investigator's laboratory, lack of knowledge or confidence about efficient methods for synthesis with multiple steps presents a significant obstacle (sometimes more so on a larger than small scale). Selection of a particular scheme from several alternatives depends on the available capabilities of the laboratory, the product desired, as well as on anticipated future requirements and need for related compounds. Many of the new reactions for organic synthesis can be applied effectively to isotopic preparations with improvement of yields and simplification of procedures compared to established classical methods. New routes developed for higher molecular weight compounds are sometimes not directly adaptable to the one-carbon analogs, either because of isolation difficulties occasioned by physical properties or by chemical reactivities peculiar to

their being first members of homologous series. Various routes for preparation of carbon-13 labeled methanol, formaldehyde, and cyanide are compared. Costs for preparations by the different methods at several scales of reaction should be carefully considered when choosing a synthetic route. Research and development expenditure to increase yields is an important, easily underestimated, economic consideration, particularly for small-scale, nonrepetitive preparations.

The building blocks from which structurally complex molecules are built are the structurally simple, low molecular weight compounds. Yet these simple structures are ones that frequently give the synthetic chemist concerned with incorporation of isotopes into particular molecular positions the most trouble. One reason is that they are so commonplace as the unlabeled varieties and so readily and cheaply available that no one has worried too much about their small-scale preparation for a century or so, except out of necessity for labeling. Many elegant schemes have been developed over the past few decades for ^{14}C ; (1) some of these are directly applicable to ^{13}C , but frequently they just will not scale up to the larger quantities encountered with stable isotopes. Another reason that the simple compounds cause trouble is that their physical properties, or those of the starting materials, often require handling techniques that may not be so familiar on a laboratory scale. This is particularly true of one-carbon compounds -- even the first members of series, they are usually a bit strange compared to their higher homologs. Sometimes their peculiar characteristics can be advantageous as well.

Some aspects of synthesis of simple ^{13}C -compounds will be discussed which should be considered by the chemist who needs to prepare these materials, either for the compounds

themselves, or as intermediates on the way to more-normal molecules having sufficient structure to be more conventionally interesting. Frequently one of the largest obstacles to carrying out a complex labeling experiment is in preparing the required simple labeled starting material. That is, obtaining the low molecular weight materials, either through synthesis carried out by themselves, by a collaborator, by a graduate student, by a technician, or however, does present a stumbling block for certain investigators. This is usually more imagined than real, and what is needed is merely some confidence building by objectively looking at the individual components of possible preparative schemes, come to a decision as to the method that appears best for the purpose and for the resources at hand, and then proceed. The problem, when present, is usually produced by economics (rather than science) -- which, after all, must be considered. And in doing this it is important to realize that the isotope, even at a thousand dollars or more per mole in its simplest chemical form, may be one of the cheaper components of the preparation.

In Fig. 1 are listed some one-carbon compounds. As ^{13}C -labeled intermediates some are more common than others. But the least utilized (whic ever that might be) may be the very one which is of the greatest important to someone's research. Some are intermediates for others, and even vice

versa, depending on particular situations; for example, formic acid can be prepared from cyanide, and cyanide can be prepared from formic acid. The last compound, on the lower right (although containing more than one carbon is functionally a one-carbon compound), is TosMIC -- an example of one of the newer reagents for organic synthesis (2) which should prove increasingly useful in labeling.

In deciding on which particular synthetic scheme to select from among several possibilities there are a number of factors to be considered (Fig. 2). There are certain requirements concerning the product and the method that must be met when the chemist sets out to prepare the compound, which will affect his choice, as well as the availability of materials, apparatus, and people with which to carry it out. The nature of the label desired, that is, which isotope at what enrichment and in which molecular site is of primary importance (of course, for one-carbon ^{13}C compounds these are automatic). Depending on the amount of product desired, certain procedures may be more desirable than others; some may not scale up, some may not scale down, and for a small amount, a low yield but quick and easy route is likely to be preferable from the economic standpoint, as well as in meeting a short deadline. Both deadlines and economics sometimes benefit when the purity requirement is realistic. For example, if product methanol

contains water, there is little point in rendering it anhydrous if it is to be carbonylated to acetic acid -- a reaction that needs water anyway. Future needs and additional uses for the product can justify a larger scale which invariably makes for lower unit cost. They can also justify, along with the possibility of future repetition, spending more development time or devising of new procedures. Since organic synthesis is, in large part, art, as well as science, the challenge presented by the problem can have quite an effect on how well the other requirements are met; esthetics can also lead to a considerable increase in unit cost, at least from the short-range viewpoint.

A preparative route that may be an obvious choice for one laboratory may be far from desirable for another. The availability of facilities, experience, and type of people to carry out the work can be very different. A laboratory that is well stocked with a variety of autoclaves and pressure vessels and people with an interest in them is more likely to carry out a reduction by catalytic hydrogenation than is a lab that has specialized in metal hydride reactions. The chemical form of available isotopic starting materials can also affect the choice of a route. For example, if labeled formic acid happens to be left over from a previous preparation, the chosen path to formaldehyde is likely to be different than if labeled methanol or carbon dioxide were to be the starting material. And, of

course, life can be simplified greatly when the particular requirements (including the aesthetics) can be satisfactorily met by a commercial source.

Perhaps the most common one-carbon intermediate is methanol. It will serve as an example in a process which is helpful in deciding among alternative synthetic schemes. One route is the hydride reduction of carbon dioxide using reagents with high boiling points, which permit easy isolation of the methanol (Fig. 3, Route A). This procedure was developed by Nystrom, Yanko, and Brown (3) in the late 1940s for ^{14}C -methanol and recently applied for the ^{13}C -analog (4). Standard apparatus and techniques found in any laboratory are used. Route B was developed for relatively large-scale preparations (probably larger by far than most individual investigators need), although it does scale down quite nicely (5). The yield is a little better, and the only work up required (if that) is removal of the mole of water.

But is the higher yield and easier procedure (once the apparatus is in operation) economically justified on the more usual laboratory scales? In Table I the cost estimates (except for the isotopic carbon dioxide) are quite crude; but it is not the absolute values that are so important as it is the comparisons, and the relative numbers should be more independent of bad guesses. Just the mechanics of actually sitting down and

preparing something like this gives additional input to the decision making process. Three scales of reaction are illustrated -- 1-, 10-, and 100-grams of methanol, and two levels of operational expense that equate to about \$10,000 and \$50,000 per man year. In this example, the two routes are not tremendously different in cost, and choice between them probably depends more on the other factors. It is obvious, however, that there is a real quantity price break, and also, that if one of the senior staff has some inexpensive technical help that can do the preparation, he can get 10 grams for less than the cost of 1 gram doing it himself. Another thing to notice is that if all that is required is 1 gram, it is a fairly safe economic gamble just to go with Route A and no trial runs. Usually though, in practice, esthetics and such matters enter in and this will not be done. The isotope is not always the most expensive thing in the pot.

Cyanide is another important and versatile intermediate. The procedure on the upper portion of Fig. 4 (6) is more adaptable to large scale or repetitive requirements in that more nonstandard equipment must be assembled. There was an unplanned fringe benefit in having a large-scale methane synthesis method already available when the requirement arose for mass-21 methane to be used in trials as an atmospheric tracer (7). The method on the lower part of Fig. 4 (8) is quite straight-

forward, using conventional equipment, but the yield is lower, HCN evolution is slow, and the crude product has to be purified by regeneration and absorption of HCN -- not too complicated, but time consuming. Hopefully, someone soon will come up with a new and nicer scheme -- perhaps based on some of the more recent methods developed for dehydrating amides to nitriles. Hydrogen cyanide is merely the nitrile corresponding to formamide, but examples are already known which work well for higher molecular weight amides, although fail for this preparation (8).

Industrial production of formaldehyde is by catalytic oxidation of methanol. Such procedures are also adaptable to a laboratory scale and have been applied to ^{13}C - and ^{14}C -formaldehydes with yields around 85 or 90% (1). Their chief disadvantage is that much development time is used in making dozens of trial runs to optimize flow rates, ratio of methanol-to-air, temperature, and so on, and almost invariably a few trials of new, different, and hopefully improved catalyst formulations. Direct reduction of carbon dioxide by lithium aluminum hydride (Fig. 5) (9) is much simpler, especially for small amounts, although the yield is lower. Reduction of the formamide (9) is also very convenient, particularly if the formate (6, 10) or formamide can also be used for other purposes, which is often the case. Whatever possibilities are

considered, the requirement as to the desired form -- whether formalin, paraformaldehyde, or the monomer -- will need to be considered.

Figure 6 illustrates a preparation of tosylmethyl isocyanide (11) (a "multi-carbon, one-carbon intermediate"). The starting material is again formate- ^{13}C for labeling at the cyanide carbon to provide a reagent useful in heterocyclic syntheses. By employing methylamine- ^{13}C the methylene carbon can be labeled. Over the past several years a variety of these new type "umpolung" reagents have been appearing which should find applications in isotopic synthesis -- not so much perhaps in introducing a single label, but in labeling a specific site in a multiply labeled compound. TosMIC, for example, can be used to prepare symmetrical and unsymmetrical ketones and 1,2-diketones, 2-hydroxyaldehydes, carboxylic acids, and nitriles (2).

One of the best ways to assure a successful, economical preparation of a labeled compound is to make use of an efficient, well-developed procedure that has been selected after careful considerations of the various requirements and specifications for the labeled product as well as of the particular capabilities that are available in the laboratory in which the preparations will be performed.

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Table 1. Comparison of Cost Estimates for Systems of Methanol-¹³C by Different Methods (Fig. 1).

Com. agent	Method	Cost (\$)					
		Method A			Method B		
Isotope		10	100	1000	10	100	1000
Asparagus, racemata		10	10	100	100	100	100
Nitrate (100 mg) (a)		10	10	100	10	100	100
(125/yr) (b)		100	100	100	100	100	100
Trifluoride (100 mg)	(a)	10	10	100	10	10	100
	(b)	100	100	100	100	100	100
Chloroform	(a)	10	10	100	10	10	10
	(b)	10	10	100	10	10	10

Legends for Figures

- Figure 1. Some one-carbon ^{13}C -labeled compounds.
- Figure 2. Factors which affect the choice of a synthetic method.
- Figure 3. Two routes to methanol- ^{13}C .
- Figure 4. Two routes to cyanide- ^{13}C .
- Figure 5. Two routes to formaldehyde- ^{13}C .
- Figure 6. Synthesis of tosylmethyl isocyanide- ^{13}C .

Figure 1

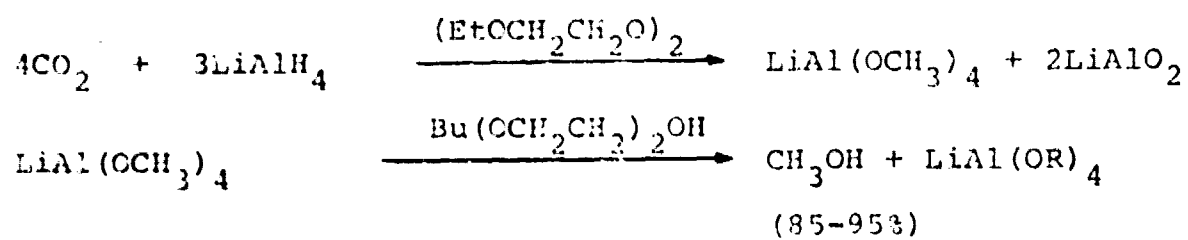
CH_3OH	NaCN	HCHO
CH_3I	KCNO	HCOOH
CH_3NH_2	KCNS	HCONH_2
CH_2N_2	H_2NCN	HCCl_3
CH_4	$(\text{H}_2\text{N})_2\text{CO}$	COCl_2
CS_2	$(\text{H}_2\text{N})_2\text{CS}$	$(\text{RO})_2\text{CO}$
COS	$(\text{H}_2\text{N})_2\text{CNH}$	TsCH_2NC

Figure 2SYNTHETIC ROUTE DETERMINANTS

<u>Requirements</u>	<u>Availability</u>
LABEL	FACILITIES
QUANTITY	EXPERIENCE
PURITY	PERSONPOWER
DEADLINE	EQUIPMENT
FUTURE	REAGENTS
ESTHETICS	COMMERCIAL

Figure 3

Route A



Route B

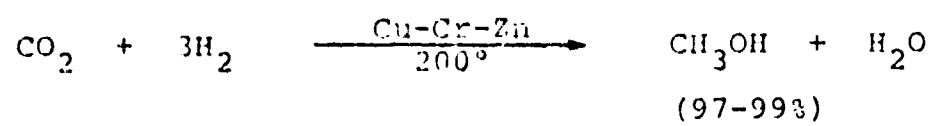


Figure 4

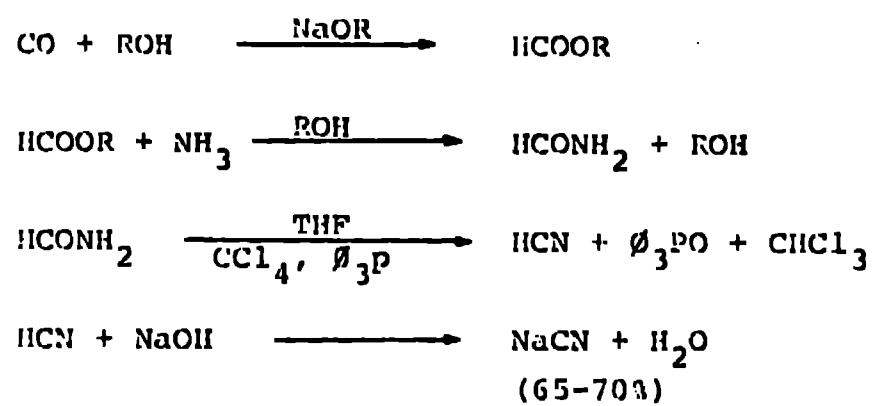
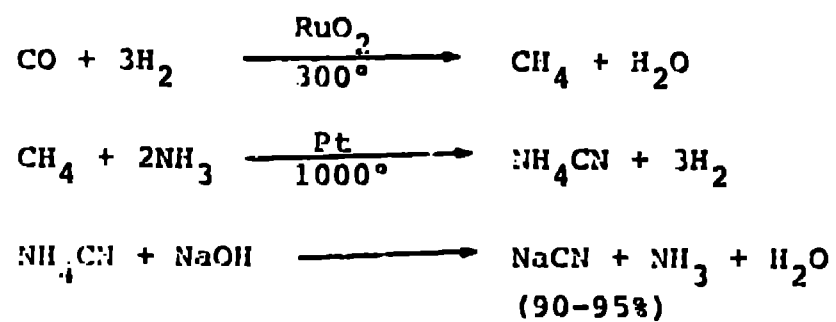


Figure 5

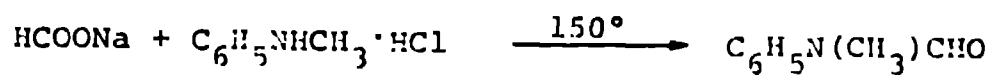
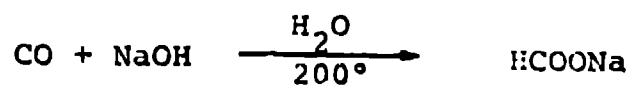
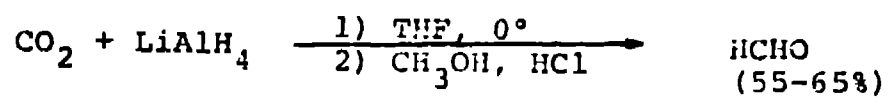


Figure 6

